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Cryo-electron microscopy reveals high-resolution structures of 30-nm chromatin fibers *in vitro*

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Human chromosomes are the largest and most visible structures involved in the transfer of genetic information. The most striking property of a chromosome is that about three billion base pairs of the human genome are compacted into a nucleus of only several micrometers in diameter. It is well known that DNA in eukaryotic cells is initially packaged into nucleosomes by means of extensive association with histone proteins. Specific interactions between individual nucleosomes drive the folding of nucleosomal arrays into 30-nm chromatin fibers and then build an entire chromosome. The hierarchical packaging of chromatin plays vital roles in the processes of DNA replication, recombination, transcription, repair and chromosome segregation. Despite intense effort for more than 30 years, high-resolution structures of 30-nm chromatin fibers remain unresolved, mainly due to the intrinsic irregularity of the native chromatin with many variations in linker length and histone modifications [1].

To solve this longstanding puzzle, Professors Zhu Ping and Li GuoHong led a unique collaborative team at the Institute of Biophysics, Chinese Academy of Sciences. After several years of efforts from optimizing sample preparation to analyzing massive data, they made a breakthrough in determining the first high-resolution structures of the 30 nm chromatin fibers by using a cutting-edge imaging technique, cryo-electron microscopy (cryo-EM) [2]. In this groundbreaking study, relatively homogenous 30 nm chromatin fibers were successfully reconstituted in the presence of linker histone H1 and with different nucleosome repeat lengths. To achieve high-resolution structures, more than 55000 images of 30 nm chromatin fibers were visually or computationally selected from about 10000 electron micrographs of frozen hydrated specimens. This highly sophisticated but tedious image process enabled them to determine 11-angstrom resolution structures of the 30 nm chromatin fibers for the first time. Importantly, the high-resolution structures reveal a novel histone dependent left-handed twist of the repeating nucleosomes and therefore provide mechanistic insights into how nucleosomes compact into higher-order chromatin fibers. Those results were published in the top journal *Science* as a research article on April 25, 2014 [2]. These elegant studies not only open a window to exploit the most fundamental processes in life: DNA replication, transcription, recombination and repair, but also represent a landmark in the use of cryo-EM for determining high-resolution structure of a macromolecular complex that has been difficult to study by other means.

Evidently, cryo-EM has emerged as one of the leading techniques to study large macromolecular assemblies and their molecular interactions in near native states. Compared to other conventional approaches (X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy), cryo-EM is particularly effective in studying heterogeneous or flexible complexes because images can be readily classified and averaged through use of sophisticated image process. As a result of many recent developments, cryo-EM has potential to revolutionize structural biology and beyond [3]. Direct electron detectors are among the most impressive developments for cryo-EM because the traditional detectors

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(charge-coupled device and photographic film) were not optimized for high-throughput and high-resolution. In contrast, the new generation of detectors offers unprecedented speed and sensitivity. Together with many other developments in sample preparation, automation and image analysis, near-atomic resolution structures of large macromolecules can now be determined by averaging hundreds of thousands of cryo-EM images [4,5]. Continuous improvements in throughput and resolution will continue to strengthen cryo-EM as a leading tool for studying chromatin and other biomedical important macromolecular machines.

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